REMARKS

Claims 14-26 are pending in the application. Claims 16-20, 22, 25, and 26 were withdrawn. Claims 14, 15, 21, 23, and 24 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement; and claims 14, 15, 21, and 24 were rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. Claims 14, 15, 21, 23, and 24 were rejected under 35 U.S.C. § 102(b) over DiCicco-Bloom et al. (U.S. Patent Application Publication No. 2002/0182729; hereafter "DiCicco-Bloom"). Each rejection is addressed below.

Amendments

Claim 14 has been amended to delete the term "preventing" and to specify, in the preamble, that the subject to be treated has thrombocytopenia.

In addition, the phrase "an inhibitor of PACAP signalling" has been replaced with "a compound inhibiting PACAP production and/or activity;" and to specify "the step of" administering the compound. Support for this amendment is found, for example, at page 9, line 29 to page 10, line 4 of the specification:

> **"Inhibition of PACAP signalling"** refers to the inhibition of the binding of PACAP or VIP to a receptor for PACAP, which includes **inhibition of the production and/or activity of the ligands PACAP** and/or VIP (PACAP or VIP inhibition by PACAP and/or VIP inhibitors) and inhibition of the production or function of one or more receptors for PACAP or the binding of PACAP or VIP thereto (PACAP receptor inhibition), e.g. by antibodies, antagonists, soluble receptors, antisense etc, as detailed herein. These molecules are also generally referred to herein as 'inhibitors of PACAP signalling.' (Emphasis added.)

Claim 15 has been amended by replacing the phrase "expressed PACAP" with "mature PACAP or an isoform thereof." Support for this amendment is found, for example, at page 7, lines 13-18 of the specification:

> **"PACAP"** refers to Pituitary Adenylate Cyclase-Activating Polypeptide

> and refers to the mature and processed versions of the **mature PACAP** as PACAP(1-48) and more particularly to processed **isoforms** PACAP(1-38)... and PACAP(1-27).... (Emphasis added.)

Claim 23 has been amended to specify the anti-PACAP antibody as a neutralizing antibody. The term "neutralizing" in the context of antibodies is recited at page 30, lines 5 to 10 of the specification:

> The role of PACAP(1-38) in thrombopoiesis was therefore further studied in control mice by subcutaneous injection of **neutralizing** polyclonal or monoclonal **anti-PACAP antibodies**. (Emphasis added).

New claims 27-32 have been added.

New claim 27 is based, in part, on previously presented claim 14, and is drawn to a method of lowering the risk of acquiring or developing thrombocytopenia in a defined subset of individuals namely those "*having a high probability of acquiring or developing thrombocytopenia.*" Support for the amendment is found, for example, at page 9, lines 17 to 22 of the specification:

> **"A subject at risk of developing thrombocytopenia"** is a subject **who has a high probability of acquiring or developing thrombocytopenia**. For example, a patient with a malignant tumour who is prescribed a chemotherapeutic treatment is at risk of developing treatment-induced thrombocytopenia and a subject who has an increased risk of exposure to infectious agents is at risk of developing infection-induced thrombocytopenia. (Emphasis added).

New claim 28 is drawn to subjects having "*cancer and wherein said compound is administered prior or during chemotherapy.*" Support for the claim is found, for example, at page 16, lines 14 to 18 of the specification:

> Alternatively, and more particularly in case of prevention of thrombocytopenia e.g. **in combination with or before chemotherapy,** administration of an inhibitor of the PACAP signalling pathway can be aimed at a maintenance of the number of active platelets (i.e. preventing a significant decrease in the number of platelets expected as a result of chemotherapy). (Emphasis added).

Subjects having cancer are described, for example, at page 16, lines 23 to 26 of the specification:

> This property of stimulating platelet production of the molecule should render it a useful adjunct in the therapy of patients suffering from acute thrombocytopenia, for example, as a result of chemo- or radiotherapy of various cancers.

New claim 29 is drawn to subjects "*at risk of developing infection-induced thrombocytopenia.*" Support is found, for example, at page 9, line 17 to 22 of the specification:

> **"A subject at risk of developing thrombocytopenia"** is a subject who has a high probability of acquiring or developing thrombocytopenia. For example, a patient with a malignant tumour who is prescribed a chemotherapeutic treatment is at risk of developing treatment-induced thrombocytopenia and a subject who has an increased risk of exposure to infectious agents is **at risk of developing infection-induced thrombocytopenia**. (Emphasis added).

New claim 30 is based, in part, on claim 19, and is drawn to the expression of PACAP and not to expression of VIP or of PACAP receptors.

New claim 31 is based, in part, on claim 21, and is drawn to antisense, RNAi, and ribozymes inhibiting PACAP expression.

New claim 32 is drawn to a neutralizing anti-PACAP antibody or antigen-binding fragment thereof, is capable of binding to PACAP(1-38). The production of antibodies against the PACAP(1-38) peptide is described in detail in Example 5 of the specification (page 30, line 30 to page 34, line 12).

No new matter has been added by the present amendment.

Applicants reserve the right to pursue any cancelled subject matter in this or a future application.

Rejection under 35 U.S.C. § 112, first paragraph - enablement

Claims 14, 15, 21, 23, and 24 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner acknowledges that specification enables "methods of treating thrombocytopenia with antibodies that bind PACAP." The Examiner also acknowledges the binding of the ligands VIP and PACAP to the receptors PACAPR, VAPC1, and VPAC2. As demonstrated by the Examples (for example, Examples 2 and 3), the administration of neutralizing antibodies (anti-PACAP) resulted in the desired therapeutic effect.

The experiments of the present invention reasonably teaches to the person skilled in the art that **any method** that lowers the effective amount of PACAP will equally result in a beneficial effect on thrombocytopenia. Accordingly, it is submitted that the specification equally enables conditions which lower the effective amount of PACAP in a subject having or being at risk for developing thrombocytopenia. Such conditions include the administration of PACAP-binding compounds such as soluble receptors or aptamers, PACAP-antagonists, or administering compounds lowering the effective concentration of expressed PACAP using, for example, antisense molecules.

Furthermore, the application provides clear instructions to assess the efficacy of claimed compounds other than antibodies, as explained at page 13, line 30 to page 14, line 4 of the specification:

> The biological activity of other potential PACAP agonists or antagonist[s] can be determined by (1) determining whether the compound binds to receptors for PACAP (Gottschall, et al. (1990) *Endocrinology* **127**, 272; EP Application 529 487) and (2) determining whether the compound stimulates the production or release of PACAP. This can be assayed on isolated platelets or megakaryocytes or can be assayed in a cell culture system wherein cells are transfected with PACAPR, VPAC1 or VPAC2.

Applicants further submit that thier specification clearly enables claim 14, as amended, with respect to anti-VIP antibodies or with respect to the blocking of receptors which can

bind PACAP. Claim 14, as amended, clearly indicates that the claimed compounds "*inhibiting production and/or activity of PACAP*" are distinct from compounds inhibiting "*the production and/or activity of VIP*" and from compounds inhibiting "*the production or function of one or more receptors for PACAP or the binding of PACAP or VIP thereto (PACAP receptor inhibition), and inhibition of the production or function of one or more receptors for PACAP or the binding of PACAP or VIP thereto (PACAP receptor inhibition).*"

In view of the above, withdrawn claim 19 and claim 21 have been amended and introduced as new claims 30 and 31, respectively, with the requirement that these claims are directed to compounds which inhibit the production and/or activity of PACAP.

Claim 23 has been amended to clarify that the claimed antibodies and fragments are **neutralizing** antibodies. The term "neutralizing" implies that the target is an active PACAP molecule. In addition, since the claim recites a method of treatment, this also implies that the antibody neutralizes a compound, which is present in the body; in other words, neutralizes a naturally-occurring molecule. Applicants submit that this amendment overcomes the rejection related to the definition of antibodies which would bind derivatives such as non-naturally occurring molecules.

Without acquiescence to the enablement rejection, Applicants introduced new claim 32 which refers to antibodies and fragments binding to the naturally occurring peptide PACAP(1-38).

New claims 27 to 29 are directed to methods of lowering the risk of acquiring or developing thrombocytopenia, aiming to improve the condition of certain subjects prior to therapy, for example, chemotherapy, in order to reduce the risk of acquiring or developing thrombocytopenia caused by the detrimental side effects of such therapy.

In view of the above amendments and comments, the enablement rejection may be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph - written description

Claims 14, 15, 21, and 24 were rejected under 35 U.S.C. § 112, first paragraph for lack of a written description.

Whereas different structurally unrelated compounds may serve as PACAP inhibitors as claimed in claim 14, Applicants refer to the passage bridging page 12 to 13 of the specification, which indicates that a wide variety of inhibitors for interfering with the PACAP signaling pathway were known in the art. Applicants further submit that, the specification provides in the earlier cited passage on page 13, instructions to assess further candidate compounds for their suitability in the claimed methods. To provide an adequate "written description," applicants need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987): "[T]he specification must 'convey clearly to those skilled in the art to whom it is addressed...the information that [the inventor] has invented the specific subject matter later claimed.'" Applicants submit that they have plainly satisfied this standard. Indeed, Applicants submit that the combination of compounds known when the application was filed and an assay to characterize such compounds convincingly teaches a skilled worker the scope of the presently claimed invention. Based on Applicants' specification, one skilled in the art would certainly recognize and appreciate that Applicants' invention encompassed the subject matter of claims 14, 15, 21, and 24, and it is this description that also allows the skilled worker to identify and recognize other compounds falling within the present claims.

Applicants further draw the attention to the fact that the claims are no longer drawn to "small molecules." Applicants further point out that the target for antisense, RNAi, and ribozymes has been amended to refer to PACAP only, and not to VIP or to one of the receptors.

Furthermore, Applicants submit that antisense, RNAi, and ribozymes are

compounds with known structure. While no **specific** structures are given for antisense RNA, RNAi, and ribozymes specific for PACAP, a skilled artisan will know how to design these as the corresponding technology was well-known prior to the filing date of the application.

In summary, the genus of enabled compounds capable of inhibiting or antagonizing PACAP is certainly broader than the (elected) species of PACAP-binding antibodies. Applicants accordingly respectfully request the rejoinder of new claims 30 and 31, and the withdrawal of this rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 14, 15, 21, 23, and 24 were rejected under 35 U.S.C. § 102(b) over DiCicco-Bloom. Claim 14 has been amended to indicate that the subject to whom the inhibitor is administered has thrombocytopenia. Applicants submit that this amendment renders this rejection moot, as DiCicco-Bloom fails to describe the treatment of thrombocytopenia.

New claims 27 to 29 are also free of this rejection as each refers to a defined group of subjects who are at known increased risk to develop thrombocytopenia. Applicants submit that the claimed subject group does not include all humans and is clearly distinct from the population described in DiCicco-Bloom, which is treated for neurological conditions.

CONCLUSION

Applicants submit the claims are in condition for allowance, and such action is hereby requested.

Transmitted herewith is a Petition to extend the period for replying to the Office Action for three months, to and including January 9, 2009 and payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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